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NOTICE OF ALLOWANCE AND FEE(S) DUE

5487 7590 04/09/2008

ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 04/09/2008

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,201	01/14/2004	Ralf Rosskamp	USAV2003/0012 US NP	3559

TITLE OF INVENTION: METHOD FOR REDUCING CARDIOVASCULAR MORBIDITY AND MORTALITY IN PREDIABETIC PATIENTS AND PATIENTS WITH TYPE 2 DIABETES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	07/09/2008

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

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If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

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Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

5487 7590 04/09/2008

ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

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(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,201	01/14/2004	Ralf Rosskamp	USAV2003/0012 US NP	3559

TITLE OF INVENTION: METHOD FOR REDUCING CARDIOVASCULAR MORBIDITY AND MORTALITY IN PREDIABETIC PATIENTS AND PATIENTS WITH TYPE 2 DIABETES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	07/09/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
BRADLEY, CHRISTINA	1654	514-003000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

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❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

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Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 04/09/2008

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 445 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 445 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	10/757,201	ROSSKAMP ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the response filed10/19/2007*.

2. ☒ The allowed claim(s) is/are *1-38 and 44-53*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Cecilia Tsang/
Supervisory Patent Examiner
Art Unit 1654

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Barbara Kurys on 3/27/2008.

The application has been amended as follows:

1. A method of treating impaired glucose tolerance (IGT) in a patient in need thereof comprising administering an effective dosage of a long acting insulin.

6. The method of claim ~~2~~1 wherein the patient has a history of one or more ~~previous serious~~ cardiovascular events or risk factors selected from the group consisting of: ~~previous~~ myocardial infarction, stroke, angina with documented ischemic changes, ~~previous~~ coronary, carotid or peripheral arterial revascularization, ~~or~~and left ventricular hypertrophy ~~by electrocardiogram or echocardiogram~~.

7. The method of claim 2 wherein the patient has one or more ~~significant~~ cardiovascular risk factors selected from the group consisting of: previous myocardial infarction, stroke, angina with documented ischemic changes, previous coronary, carotid or peripheral arterial revascularization, ~~or~~and left ventricular hypertrophy ~~by electrocardiogram or echocardiogram~~.

8. A method of treating impaired fasting glucose (IFG) in a patient in need thereof comprising administering an effective dosage of a long acting insulin.

13. The method of claim ~~9~~8 wherein the patient has a history of one or more ~~previous serious~~ cardiovascular events or risk factors selected from the group consisting of: ~~previous~~ myocardial infarction, stroke, angina with documented ischemic changes, ~~previous~~ coronary, carotid or peripheral arterial revascularization, ~~or~~and left ventricular hypertrophy ~~by electrocardiogram or echocardiogram~~.

14. The method of claim 9 wherein the patient has one or more ~~significant~~ cardiovascular risk factors selected from the group consisting of: previous myocardial infarction, stroke, angina with documented ischemic changes, previous coronary, carotid or peripheral arterial revascularization, ~~or~~and left ventricular hypertrophy ~~by electrocardiogram or echocardiogram~~.

15. A method of treating early Type 2 diabetes in a patient in need thereof comprising administering an effective dosage of a long acting insulin.

20. The method of claim ~~16~~15 wherein the patient has a history of one or more ~~previous serious~~ cardiovascular events or risk factors selected from the group consisting of: ~~previous~~ myocardial infarction, stroke, angina with documented ischemic changes, ~~previous~~ coronary, carotid or peripheral arterial revascularization, ~~or~~and left ventricular hypertrophy ~~by electrocardiogram or echocardiogram~~.

21. The method of claim 16 wherein the patient has one or more ~~significant~~ cardiovascular risk factors selected from the group consisting of: previous myocardial infarction, stroke, angina with documented ischemic changes, previous coronary, carotid or peripheral arterial revascularization, ~~or~~and left ventricular hypertrophy ~~by electrocardiogram or echocardiogram~~.

29. A method of treating atherosclerosis in a patient diagnosed with a disease or condition selected from the group consisting of IFG, IGT, and early Type 2 diabetes ~~or Type 2 diabetes~~, comprising administering an effective dosage of a long acting insulin.

34. A method of improving endothelial function in a patient diagnosed with a disease or condition selected from the group consisting of IFG, IGT, and early Type 2 diabetes ~~or Type 2 diabetes~~, comprising administering an effective dosage of a long acting insulin.

Cancel claims 39-43.

44. A method of improving left ventricular diastolic and systolic function in a patient diagnosed with a disease or condition selected from the group consisting of IFG, IGT, and early Type 2 diabetes ~~or Type 2 diabetes~~, comprising administering an effective dosage of a long acting insulin.

49. A method of reducing blood glucose levels in a patient diagnosed with a disease or condition selected from the group consisting of IFG, IGT, and early Type 2 diabetes ~~or Type 2 diabetes~~, comprising administering an effective dosage of a long acting insulin.

Cancel claims 54-58.

Replace the paragraph beginning on page 8, line 4, with the following paragraph:

Lantus® LANTUS (insulin glargine) is a recombinant human insulin analog that is a long-acting (up to 24-hour duration of action), parenteral blood-glucose lowering agent.[39] The post-marketing surveillance safety database experience reveals no increased incidence of hypoglycemia or unexpected adverse reactions compared to other marketed insulin preparations.

In a multiple-dose pharmacokinetic study, Lantus® LANTUS (insulin glargine) levels were shown to reach steady-state after 2 doses (2 days) of treatment (Study 1020). Treatment with Lantus® insulin LANTUS (insulin glargine) offers the possibility of a smooth, daylong, blood insulin profile without a definite peak that can be finely titrated to lower subjects' FPG in a durable manner, while minimizing the risk of hypoglycemia at other times of day.

Replace the paragraph beginning on page 9, line 9, with the following paragraph:

The ideal basal insulin might be expected to be less worrisome from this standpoint because the circulating insulin produced would target blood glucose elevations throughout the day rather than mealtime fluctuations. It would not demonstrate notable peaks in plasma level, and in consequence the tendency to produce hypoglycemia would be less than with peaked insulins. The "Treat-to-Target" study [38] in US/Canada type 2 diabetic patients investigated whether a single bedtime dose of Lantus® LANTUS (insulin glargine) vs NPH insulin (a moderate- to long-acting insulin with a pronounced peak in plasma activity for 4 to 8 hours after injection)[39] would achieve target metabolic control without increasing nocturnal hypoglycemia. The trial was successful in demonstrating both its primary objective (more Lantus® LANTUS (insulin glargine) -treated patients than NPH-treated patients reaching target HbA1c [<= 7%] without nocturnal hypoglycemia), but also showed significant reductions in nocturnal hypoglycemia vs NPH in all patients.

Replace the paragraph beginning on page 10, line 1, with the following paragraph:

Insulin treatment has been demonstrated to reduce CV morbidity and mortality in a population with more advanced diabetes, and offers this prediabetic population the possibility of reducing cardiovascular risk through effective reductions in blood glucose and free fatty acid levels, and in the associated tissue damage resulting from their chronic elevations. The availability of Lantus® insulin LANTUS (insulin glargine) creates the possibility of treating subjects with widely-varying degrees of dysglycemia with the effectiveness of insulin over a 24 hour period while minimizing the risk of hypoglycemia (especially hypoglycemia seen in association with exercise) inherent in earlier insulin preparations with more distinct peak effects.

Replace the paragraph beginning on page 14, line 18, with the following paragraph:

Study HOE901-1021 was conducted to test the safety, efficacy, and tolerability of Lantus® LANTUS (also known as HOE901 and insulin glargine) in treating individuals with IGT, IFG, and mild diabetes. As stated earlier, this patient population is at high risk for CV disease.

Replace the paragraph beginning on page 18, line 26, with the following paragraph:

Thus in this study it was possible to use Lantus® LANTUS (insulin glargine) to treat the mildly hyperglycemic subjects to normoglycemic levels without hypoglycemia in relation to

exercise. These data have prompted the undertaking of a large intervention trial, the ORIGIN study, wherein it is expected that Lantus® LANTUS (insulin glargine) will be shown to be efficacious in reducing CV disease, with low risk for producing hypoglycemic side effects in relation to the exercise which forms a cornerstone of the glucose management of these individuals. The ORIGIN study will randomly allocate approximately 10,000 subjects with IGT, IFG, or early type 2 diabetes at risk for cardiovascular morbidity (because of a history of previous serious cardiovascular events, or because of significant cardiovascular risk factors) either to treatment with a single injection of Lantus® LANTUS (insulin glargine) per day, titrated to produce a FPG of 95 mg/dL or less without hypoglycemia, or to standard treatment of each condition. Examples of serious cardiovascular events include, but are not limited to, previous myocardial infarction, stroke, angina with documented ischemic changes, previous coronary, carotid or peripheral arterial revascularization, or left ventricular hypertrophy by electrocardiogram or echocardiogram. Examples of significant cardiovascular risk factors include, but are not limited to, previous myocardial infarction, stroke, angina with documented ischemic changes, previous coronary, carotid or peripheral arterial revascularization, or left ventricular hypertrophy by electrocardiogram or echocardiogram. This standard treatment plan includes a stepped-care algorithm for the institution of therapy in subjects who are either diabetic at baseline, or who become so during the trial. Monitoring of, and treatment intervention in, these control subjects will occur in a manner that is at least as aggressive as that recommended by currently-accepted standards of care (e.g. ADA guidelines). The morbidity/mortality study will be multicenter, international, randomized, and open-label, with a mean treatment duration of 5 years. The primary outcome variable is a composite cardiovascular endpoint of cardiovascular

deaths, nonfatal MI and stroke, revascularization, hospitalization for heart failure CHF, and unstable angina. Secondary variables include all-cause mortality and rates of development or progression of microvascular disease. A separate investigation will examine the progression to type 2 diabetes in the IGT and IFG subjects treated with Lantus® LANTUS (insulin glargine) versus usual care.

Replace the paragraph beginning on page 19, line 22, with the following paragraph:

Despite the novelty of the treatment paradigm proposed for the ORIGIN study, it is believed that hypoglycemia will be minimal based on several factors:

1. The 24-hour plasma insulin profile without a definite peak resulting from Lantus® LANTUS (insulin glargine) administration, decreasing the vulnerability of patients to excessive insulin concentrations which have historically occurred at unpredictable times during the day, and to unpredictable degrees, with other insulin preparations.
2. The gradual dose titration scheme proposed for the study. Lantus® LANTUS (insulin glargine) doses will start low, from 2-6 IU per day and the insulin administered will be distributed over a 24-hour period. Dose increases will be small, and made only after FPG levels from previous doses have reached steady-state.
3. The goal of Lantus® LANTUS (insulin glargine) titration is a target FPG of 95 mg/dL. This is at the upper end of the normal range for subjects without diabetes. Many IGT subjects in this trial will have an FPG in the target range from the start of the study, and if assigned to receive Lantus® LANTUS (insulin glargine) will consequently receive the starting dose only.

In any case, the risk of nocturnal hypoglycemia resulting from Lantus® LANTUS (insulin glargine) administration which has reduced FPG to the vicinity of 95 mg/dL should be minimal, especially since most of these subjects will exhibit a degree of decreased insulin sensitivity.

4. Subjects will be asked to monitor their blood glucose at home especially during titration, to detect any tendency to hypoglycemia in that setting (peri-exercise, after missed meals, overnight).

Replace the paragraph beginning on page 19, line 10, with the following paragraph:

The results of the 1021 Study which confirmed the safety and tolerability of Lantus® LANTUS (insulin glargine) in drug-naïve type 2 diabetes patients as well as in prediabetic individuals, also support Lantus' LANTUS' (insulin glargine) special usefulness in patients with moderate to severe DDL.

Replace the paragraph beginning on page 20, line 14, with the following paragraph:

Insulin has features that make it especially useful in the patient with pronounced diabetic dyslipidemia, as compared to the oral antidiabetic agents usually used as initial pharmacotherapy. The "Treat-to-Target" study (HOE901/4002) of Lantus LANTUS (insulin glargine) in a type 2 diabetic population inadequately treated with oral drugs was notable in demonstrating the success of Lantus LANTUS (insulin glargine) and its comparator, NPH

insulin, in reducing blood glucose levels to target levels in the majority of randomized patients. NPH insulin despite having a prolonged duration of action, has a pronounced peak effect from 3 – 6 hours after injection, rendering it less suitable in the management of the patient with milder diabetes due to the risk for hypoglycemia. Indeed even in this more severely diabetic population Lantus LANTUS (insulin glargine) demonstrated significant advantages over NPH in hypoglycemia, especially nocturnal hypoglycemia.

Replace the paragraph beginning on page 20, line 25, with the following paragraph:

As a consequence of the excellent glycemic control attained, which set the standard for glycemic control in future trials, the 4002 study results are especially useful as an assessment of Lantus's LANTUS' (insulin glargine) effects on lipids. The effects of Lantus LANTUS (insulin glargine) in the population of the "treat-to-target" 4002 study on fasting TG levels increased with the magnitude of baseline TG elevations: reductions of 24%, 34%, and 38% were seen in fasting TG levels with, respectively, all patients; those with fasting TG in the 300 – 499 mg/dL range (13% of the 4002 population); and those with elevations of 500 mg/dL or more (another 8% of the 4002 population). It is also notable that highly statistically significant reductions in non-HDL-cholesterol (see below) were seen in the two pooled treatments in the 4002 study, greater in magnitude the higher the baseline level of TG.

Replace the paragraph beginning on page 21, line 4, with the following paragraph:

There is evidence from the literature that use of sulfonylurea (SU) as initial drug treatment of the type 2 patient with DDL exerts a weaker effect on reduction of hypertriglyceridemia, or on increasing HDL-C, than is seen with insulin, and/or that the effects are less durable. In order to compare the effects of Lantus LANTUS (insulin glargine) on fasting TG and non-HDL-C levels with oral agents from the sulfonylurea class, the glimepiride (Amaryl®AMARYL) database at Aventis was examined. Both multicenter placebo-controlled studies in the Amaryl ® AMARYL (glimepiride) registration database demonstrated a more modest effect of Amaryl® AMARYL (glimepiride) on both TG and non-HDL-C concentrations than Lantus LANTUS (insulin glargine) demonstrated in the 4002 study, despite a prominent effect of Amaryl® AMARYL (glimepiride) to lower blood glucose. These results are shown in Table 1 below for patients with various levels of fasting hypertriglyceridemia.

Replace the paragraph beginning on page 23, line 3, with the following paragraph:

The lipid-lowering effects of metformin are variable depending on the study and clinical setting, but while the TG-lowering and HDL-increasing effects of metformin are generally superior to SU, they do not exceed the effects of insulin quoted above. Thiazolidinediones (TZDs) differ in their effects – pioglitazone is associated with notable beneficial effects on the abnormalities of DDL, whereas rosiglitazone seems to have almost no effect on these parameters (confirmed significantly inferior to Lantus LANTUS (insulin glargine) in Study 4014, which compared Lantus ® LANTUS (insulin glargine) and rosiglitazone in type 2 diabetic patients already treated with other oral antidiabetic drugs – see Table 2 below).

Replace the paragraph beginning on page 25, line 2, with the following paragraph:

The special advantages of insulin in the treatment of diabetic dyslipidemia, which along with insulin's established effectiveness in blood glucose control, suggest that it is a preferred treatment compared to available oral antidiabetic drugs. Until recently, the drug treatment of blood glucose elevations in drug-naïve diabetic patients has consisted of oral antidiabetic agents because of a fear of hypoglycemia from the use of insulin in this population. The novel development is the availability of Lantus® LANTUS (insulin glargine), the first truly basal insulin, which by virtue of its flat pharmacokinetic profile and 24-hour duration of action, can supply a steady insulin effect with low risk for hypoglycemia due to the lack of a pronounced peak effect. Because of this, insulin treatment of the diabetic patient previously treated with lifestyle measures only, is possible, and thus insulin treatment of patients in this category with pronounced diabetic dyslipidemia is possible, to reduce their elevated blood lipid values as well as their elevated blood glucose values.

Replace the paragraph beginning on page 27, line 2, with the following paragraph:

As used herein, the term "long acting insulin" is an insulin analog that is a long acting (up to 24-hour duration of action) blood glucose lowering agent. Such long acting insulins include, but are not limited to, Lantus® LANTUS (insulin glargine), NPH, Lente® LENTE human insulin zinc suspension [rDNA origin], Ultralente®ULTRALENTE human insulin extended

zinc suspension [rDNA origin], and Semilente® SEMILENTE (prompt insulin zinc suspension).

Amend Table 1 on page 22 as indicated by the replacement sheet submitted herewith.

Amend Table 2 on page 24 as indicated by the replacement sheet submitted herewith.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Friday, 9:00 A.M. to 3:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Christina Marchetti Bradley/
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654